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Association between hiatal hernia and Barrett's esophagus: an updated meta-analysis with trial sequential analysis

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Abstract

Background: Barrett's esophagus (BE) is a precursor of esophageal adenocarcinoma. It is critical to recognize the risk factors associated with BE.

Objectives: The present meta-analysis aims to systematically estimate the association of hiatal hernia with the risk of BE.

Design: A meta-analysis with trial sequential analysis.

Data sources and methods: The PubMed, EMBASE, and Cochrane Library databases were searched. The pooled odds ratios (ORs) and adjusted ORs (aORs) with their 95% confidence intervals (CIs) were calculated for the combined estimation of unadjusted data and data adjusted for confounders, respectively. Heterogeneity was quantified using the Cochrane Q test and I^2 statistics. Subgroup, meta-regression, and leave-one-out sensitivity analyses were employed to explore the sources of heterogeneity.

Results: Forty-seven studies with 131,517 participants were included. Based on the unadjusted data from 47 studies, hiatal hernia was significantly associated with an increased risk of any length BE (OR = 3.91, 95% CI = 3.31–4.62, $p < 0.001$). The heterogeneity was significant ($I^2 = 77\%$; $p < 0.001$) and the definition of controls ($p = 0.014$) might be a potential contributor to heterogeneity. Based on the adjusted data from 14 studies, this positive association remained (aOR = 3.26, 95% CI = 2.44–4.35, $p < 0.001$). The heterogeneity was also significant ($I^2 = 65\%$; $p < 0.001$). Meta-analysis of seven studies demonstrated that hiatal hernia was significantly associated with an increased risk of long-segment BE (LSBE) (OR = 10.01, 95% CI = 4.16–24.06, $p < 0.001$). The heterogeneity was significant ($I^2 = 78\%$; $p < 0.001$). Meta-analysis of seven studies also demonstrated that hiatal hernia was significantly associated with an increased risk of short-segment BE (OR = 2.76, 95% CI = 2.05–3.71, $p < 0.001$). The heterogeneity was not significant ($I^2 = 30\%$; $p = 0.201$).

Conclusion: Hiatal hernia should be a significant risk factor for BE, especially LSBE.

Registration: PROSPERO registration number CRD42022367376.

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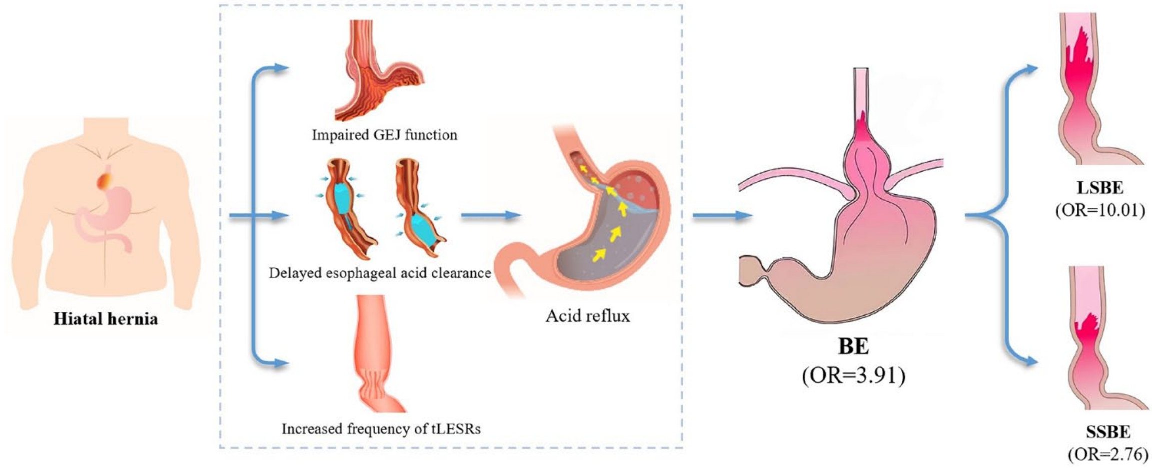

Graphical abstract

Keywords: Barrett's esophagus, esophageal adenocarcinoma, gastroesophageal reflux disease, hiatal hernia, meta-analysis

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Introduction

Barrett's esophagus (BE), a major complication of gastroesophageal reflux disease (GERD), is defined as an abnormal condition in which normal esophageal squamous epithelium has been replaced by columnar-lined epithelium with histological evidence of specialized intestinal metaplasia.[1] BE is the only known precursor lesion for the development of esophageal adenocarcinoma (EAC). It is estimated that about 0.33% of BE individuals progress to EAC annually worldwide[2] and the risk of EAC among BE patients is 10- to 55-fold higher as compared to the general population.[3] BE is usually asymptomatic in nature and can only be diagnosed by endoscopy, therefore, its estimated prevalence in the population remains difficult to assess.[4] Existing risk factors for BE include gastroesophageal reflux symptoms, male, age greater than 50 years, white race, increased body mass index, and/or central adiposity, smoking, and family history.[1,5–8]

Hiatal hernia is a common digestive disease with acid regurgitation, heartburn, and chest pain as the predominant manifestations, which refers to protrusion of stomach or other abdominal viscera through the esophageal hiatus of the diaphragm into the mediastinum.[9] It has been divided into four types based on the currently recognized anatomical classification. Type 1 hiatal hernia is the most prevalent type, accounting for more than 90% of cases of hiatal hernia, also termed a sliding hiatal hernia; and types 2–4 refer to paraesophageal hernia.[10] Hiatal hernia has been recognized as an important pathophysiology of GERD and strongly correlates with BE.[10] To the best of our knowledge, only one meta-analysis, which was published in 2013, systematically reviewed the effect of hiatal hernia on BE.[11] Nevertheless, since then, numerous individual studies have been published. Furthermore, this previous meta-analysis had a major drawback that patients with endoscopically suspected BE or an irregular *Z* line as a control group were not explicitly excluded, thereby underestimating the effect of hiatal hernia on BE. Consequently, we have conducted an updated meta-analysis to more comprehensively and precisely determine the clinical significance of hiatal hernia on the risk of BE by combining the most recent evidence.

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The PRISMA checklist was shown in Supplemental Material.

Registration

This study was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with a registration number of CRD42022367376.

Literature search

All relevant articles reporting the prevalence of hiatal hernia in patients with and without BE were searched *via* PubMed, EMBASE, and Cochrane Library databases. The search items were as follows: ('hiatal hernia' OR 'hiatus hernia') AND ('Barrett esophagus' OR 'Barrett' OR 'Barrett metaplasia' OR 'Barrett oesophagus'). The last search was conducted on 16 October 2022.

Selection criteria

Inclusion criteria were as follows: (1) observational (case–control or cross-sectional or cohort) studies; (2) BE should be confirmed by endoscopy with biopsies; (3) studies should compare the prevalence of hiatal hernia between participants with and without BE; (4) all participants should be older than 18 years; and (5) studies should be published in English. In case of multiple publications based on the same dataset, one publication with the most updated or inclusive data was given precedence.

Exclusion criteria were as follows: (1) duplicated studies; (2) reviews and meta-analyses; (3) case reports; (4) guidelines, consensus, or reports; (5) editorials, comments, letters, or notes; (6) experimental or animal studies; (7) studies published in the form of abstracts; (8) studies did not explore the association between hiatal hernia and BE; (9) participants included patients with endoscopically suspected BE or an irregular *Z* line; (10) participants were younger than 18 years old; (11) studies were not published in English; (12) overlapping participants among studies; (13) absence of relevant data; and (14) full texts could not be obtained.

Data extraction

The following data were extracted: first author, publication year, country, study design, diagnostic criteria for BE, diagnostic timing of BE, segment lengths of BE, definition of control groups, number of participants in case and control groups, and prevalence of hiatal hernia in the two groups. In addition, adjusted odds ratios (aORs) with 95% confidence intervals (CIs) and adjusted confounders were also extracted from the studies, in which multivariate regression analyses were performed to further evaluate the association of hiatal hernia with BE. Two investigators (SM and YH) independently extracted the data from the included studies, and any disagreement was resolved by discussion or consultation with a third investigator (XQ).

Study quality assessment

The quality of included case–control and cohort studies was assessed using the Newcastle–Ottawa Scale (NOS), which evaluates the quality of studies in the parts of selection (four points), comparability (two points), and exposure (three points). The maximum NOS score is 9. A score of 0–3, 4–6, and 7–9 represents low, moderate, and high quality, respectively. The quality of included cross-sectional studies was assessed using an 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ). An item is scored '1', if the study being assessed clearly answers the question, which is marked as a 'yes'; otherwise, it is scored '0'. The maximum AHRQ score is 11. A score of 0–3, 4–7, and 8–11 represents low, moderate, and high quality, respectively. Two investigators (SM and YH) independently evaluated the quality of the included studies, and any disagreement was resolved by discussion or consultation with a third investigator (XQ).

Statistical analyses

Meta-analyses were performed *via* Review Manager software (Version 5.4, Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark), Stata software (Version 12.0, Stata Corp, College Station, TX, USA), and trial sequential analysis (TSA) software (Version 0.9.5.10, CTU, Centre for Clinical Intervention Research, Copenhagen, Denmark). A random-effects model was adopted to calculate the combined results and forest plots were generated for a visual display of outcome of individual studies.[12] Meta-analyses were separately performed among the studies with and without adjustment for confounders. Odds ratios (ORs) with 95% CIs were calculated for the combined estimation of unadjusted data, and aORs with

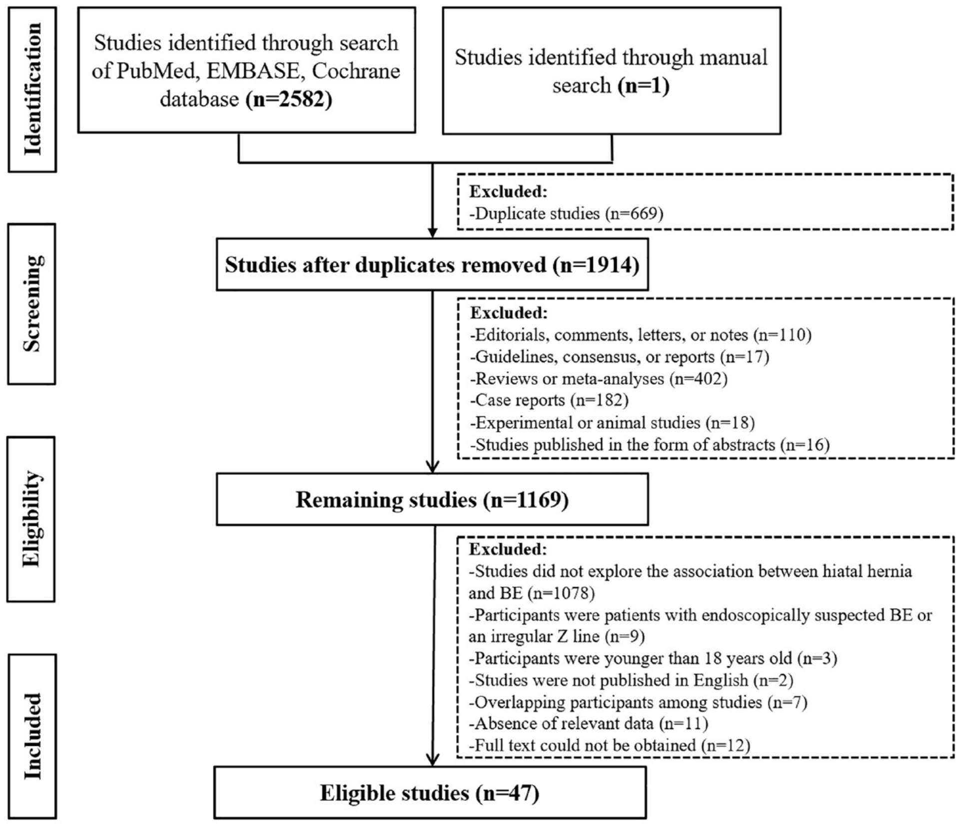

Figure 1. A flowchart of study inclusion.

95% CIs were calculated for the combined estimates of data adjusted for confounders. The Cochrane Q test and I^2 statistics were conducted to assess the heterogeneity.[13,14] $I^2 > 50\%$ and/or $p < 0.1$ were considered to have statistically significant heterogeneity. TSA was conducted to assess the reliability and stability of cumulative evidence by minimizing type I error and random error.[15,16] The required information size (RIS) was calculated based on a two-sided 5% risk of a type I error, 20% risk of a type II error (power of 80%), and pooled event rates in case and control groups. The trial sequential monitoring boundaries were computed using the O'Brien–Fleming approach. Subgroup analyses were planned according to the definition of controls, study design, publication year, region, sample size, diagnostic criteria for BE, diagnostic timing of BE, and adjustment for confounders to investigate the source of heterogeneity. The interaction between subgroups was assessed. Meta-regression analyses were also grouped based on the aforementioned variables.[17] Leave-one-out sensitivity analyses were employed with the removal of each study once to assess whether any single study could affect the overall result.[14] Egger test was employed to check the publication bias, and $p < 0.1$ indicated significant publication bias.[18]

Results

Study selection

Overall, 2582 studies were searched from the PubMed, EMBASE, and Cochrane Library databases, and one study from hand-searching. Of them, 47 with a total of 131,517 participants were eligible for final review and included in this meta-analysis (Figure 1).

Study characteristics

The detailed characteristics of included studies are presented in Table 1 and Supplemental Table 1. Among them, 17 studies were case–control studies, 2 were cohort studies, and 28 were cross-sectional studies. They were published between 1985 and 2022. Sixteen studies were performed

Table 1. Summary of study characteristics.

First author (year)	Country	Study design	Diagnostic criteria for BE	Diagnostic timing of BE	Length of BE	Definition of controls	Number of cases/ controls	Prevalence of hiatal hernia	
								Cases	Controls
Farha (2022)	USA	Cohort	IM	Previously	Any	Without BE on endoscopy	21/302	19/21	97/302
Okereke (2021)	USA	Cohort	NA	Previously and newly	Any	GERD	34/40	15/29	14/40
Asreah (2021)	Iraq	Cross-sectional	IM	NA	Any	GERD and NEJ	13/126	7/13	8/126
						GERD	13/47		5/47
						NEJ	13/79		3/79
Alsahafi (2021)	Saudi Arabia	Cross-sectional	IM	NA	Any	Without BE on endoscopy	9/2787	4/9	832/2787
Quach (2020)	Vietnam	Cross-sectional	CM	NA	Any	Without BE on endoscopy	47/1900	8/47	36/1900
Hadi (2020)	USA	Case–control	IM	NA	Any	Without BE on endoscopy	107/984	33/107	280/984
Alkhayyat (2020)	USA	Case–control	IM	NA	Any	Without BE on endoscopy	18/846	3/18	22/846
Chen (2019)	China	Cross-sectional	IM	NA	Any	Without BE on endoscopy	89/3296	71/89	1739/3296
Erridge (2018)	UK	Case–control	NA	NA	Any	GERD	2119/42,356	1146/2119	8900/42,356
Bazin (2018)	France	Case–control	IM	NA	Any	GERD	100/101	58/100	26/101
Baik (2017)	USA	Case–control	IM	Previously	Any	Without BE on endoscopy	31/27	23/31	6/27
Suna (2016)	Turkey	Cross-sectional	IM	Newly	Any	Without BE on endoscopy	18/2683	8/18	135/2683
Shiota (2016)	USA	Cross-sectional	IM	NA	Any	Without BE on endoscopy	263/1416	227/263	890/1416
Dore (2016)	Italy	Cross-sectional	IM	Newly	Any	Without BE on endoscopy	133/5023	69/131	2206/5023
Di Caro (2016)	UK	Case–control	CM	Previously and newly	Any	GERD and no-GERD	250/224	141/250	45/224
						GERD	250/28		9/28
						No-GERD	250/196		36/196
Sharifi (2014)	Iran	Cross-sectional	IM	NA	Any	Without BE on endoscopy	34/702	14/34	267/702
Ren (2014)	USA	Case–control	CM	Previously	Any	GERD	109/223	70/109	97/223

(Continued)

Table 1. (Continued)

First author (year)	Country	Study design	Diagnostic criteria for BE	Diagnostic timing of BE	Length of BE	Definition of controls	Number of cases/controls	Prevalence of hiatal hernia	
								Cases	Controls
Pascarenco (2014)	Romania	Cross-sectional	IM	NA	Any	Without BE on endoscopy	24/218	11/24	60/218
					LSBE		2/218	1/2	
					SSBE		17/218	7/17	
					USSBE		5/218	3/5	
Pohl (2013)	Germany	Case–control	NA	NA	Any	GERD and no-GERD	162/301	76/162	79/301
						GERD	162/188		54/188
						No-GERD	162/113		25/113
Nason (2013)	USA	Cross-sectional	IM	Newly	Any	Without BE on endoscopy	33/245	25/33	129/245
Katsinelos (2013)	Greece	Cross-sectional	IM	NA	Any	Without BE on endoscopy	75/1915	16/75	180/1915
Yin (2012)	China	Cross-sectional	IM	NA	Any	GERD	32/496	10/32	40/496
Mathew (2011)	India	Cross-sectional	CM	NA	Any	GERD	46/232	11/46	14/232
Jonaitis (2011)	Lithuania	Cross-sectional	IM	NA	Any	GERD	33/160	33/33	142/160
Xiong (2010)	China	Cross-sectional	IM	NA	Any	Without BE on endoscopy	21/2001	1/21	28/2001
Kuo (2010)	China	Cross-sectional	IM	NA	Any	GERD	13/331	7/13	31/331
Peng (2009)	China	Cross-sectional	IM	NA	Any	Without BE on endoscopy	27/2553	3/27	43/2553
Odemis (2009)	Turkey	Cross-sectional	IM	Newly	Any	Without BE on endoscopy	12/988	7/12	43/988
Lord (2009)	USA	Case–control	IM	NA	Any	Without BE on endoscopy	44/116	37/44	70/116
Park (2009)	Korea	Cross-sectional	IM	NA	Any	Without BE on endoscopy	215/23,350	28/215	619/23,350
Ringhofer (2008)	Austria	Cross-sectional	IM	Newly	Any	GERD	19/83	11/19	14/83
Moons (2008)	Netherlands	Case–control	IM	Previously and newly	Any	GERD	255/247	217/255	161/247
Tseng (2008)	China	Cross-sectional	CM	NA	Any	GERD and no-GERD	12/19,776	1/12	157/19,776
						GERD	12/3129		31/3129
						No-GERD	12/16,647		126/16,647

(Continued)

Table 1. (Continued)

First author (year)	Country	Study design	Diagnostic criteria for BE	Diagnostic timing of BE	Length of BE	Definition of controls	Number of cases/ controls	Prevalence of hiatal hernia	
								Cases	Controls
Lee (2008)	China	Case–control	IM	NA	Any	GERD	21/28	15/21	16/28
Koek (2008)	Belgium	Cross-sectional	IM	NA	Any	GERD	30/392	14/30	141/392
Sgouros (2007)	Greece	Case–control	IM	Newly	Any	GERD and no-GERD	17/846	15/17	458/846
						GERD	17/597		405/597
						No-GERD	17/249		53/249
Rajendra (2007)	Malaysia	Case–control	CM	Previously	Any	GERD and no-GERD	55/133	29/55	11/133
					LSBE		30/133	22/30	
					SSBE		25/133	7/25	
					Any	GERD	55/80	29/55	10/80
					LSBE		30/80	22/30	
					SSBE		25/80	7/25	
					Any	No-GERD	55/53	29/55	1/53
					LSBE		30/53	22/30	
					SSBE		25/53	7/25	
Veldhuyzen van Zanten (2006)	Canada	Cross-sectional	IM	Newly	Any	Without BE on endoscopy	25/1015	7/25	228/1015
Toruner (2004)	Turkey	Cross-sectional	IM	Newly	Any	Without BE on endoscopy	29/366	19/29	129/366
Rajendra (2004)	Malaysia	Cross-sectional	IM	NA	Any	GERD and no-GERD	123/1862	33/123	123/1862
						GERD	123/121		17/121
						No-GERD	123/1741		106/1741
Nasseri-Moghaddam (2003)	Iran	Cross-sectional	CM	Newly	Any	GERD	68/139	53/68	98/139
					LSBE		10/139	8/10	
					SSBE		58/139	45/58	
Conio (2002)	Italy	Case–control	IM	Newly	Any	GERD and no-GERD	149/451	83/147	85/451
						GERD	149/143		64/143
						No-GERD	149/308		21/308

(Continued)

Table 1. (Continued)

First author (year)	Country	Study design	Diagnostic criteria for BE	Diagnostic timing of BE	Length of BE	Definition of controls	Number of cases/ controls	Prevalence of hiatal hernia	
								Cases	Controls
Campos (2001)	USA	Case–control	IM	NA	Any	GERD	174/328	150/174	183/328
					LSBE		107/328	101/107	
					SSBE		67/328	49/67	
Avidan (2001)	USA	Case–control	IM	NA	Any	NEJ	1016/3047	588/1016	803/3047
					LSBE		366/3047	230/366	
					SSBE		650/3047	358/650	
Cameron (1999)	USA	Case–control	IM	Previously	Any	GERD and no-GERD	64/103	57/64	43/103
					LSBE		46/103	44/46	
					SSBE		18/103	13/18	
					Any	GERD	64/31	57/64	22/31
					LSBE		46/31	44/46	
					SSBE		18/31	13/18	
					Any	No-GERD	64/72	57/64	21/72
					LSBE		46/72	44/46	
					SSBE		18/72	13/18	
Byrne (1999)	UK	Cross-sectional	CM	Previously	Any	Without BE on endoscopy	23/194	17/23	59/194
					LSBE		8/194	8/8	
					SSBE		15/194	9/15	
Sarr (1985)	USA	Cross-sectional	CM	NA	Any	Without BE on endoscopy	44/318	31/44	152/318

BE, Barrett's esophagus; CM, columnar metaplasia; GERD, gastroesophageal reflux disease; IM, intestinal metaplasia; LSBE, long-segment BE; NEJ, normal esophagogastric junction; SSBE, short-segment BE; USSBE, ultrashort-segment BE.

in Asia,[19–34] 16 in Europe,[35–50] 14 in America,[51–64] and 1 in Oceania.[65]

Study quality

Among the case–control and cohort studies, 15 and 4 were of moderate and high quality, respectively (Supplemental Table 2). Among the cross-sectional studies, 24 and 4 were of moderate and high quality, respectively (Supplemental Table 3).

Hiatal hernia and any length BE

Based on the unadjusted data from 17 case–control, 2 cohort, and 28 cross-sectional studies, the meta-analysis demonstrated a significantly higher prevalence of hiatal hernia in patients with BE than those without (OR = 3.91, 95% CI = 3.31–4.62, $p < 0.001$). The heterogeneity was statistically significant ($I^2 = 77\%$; $p < 0.001$) (Figure 2). According to TSA, the cumulative Z-curves crossed the conventional test boundary and TSA boundary, and the total sample size surpassed the RIS ($n = 1022$) as well, indicating that there was enough evidence to conclude a significant association of hiatal hernia with an increased risk of any length BE (Supplemental Figure 1). Results of subgroup analyses were shown in Table 2. Such a statistically significant association between them disappeared in the subgroup analyses of cohort

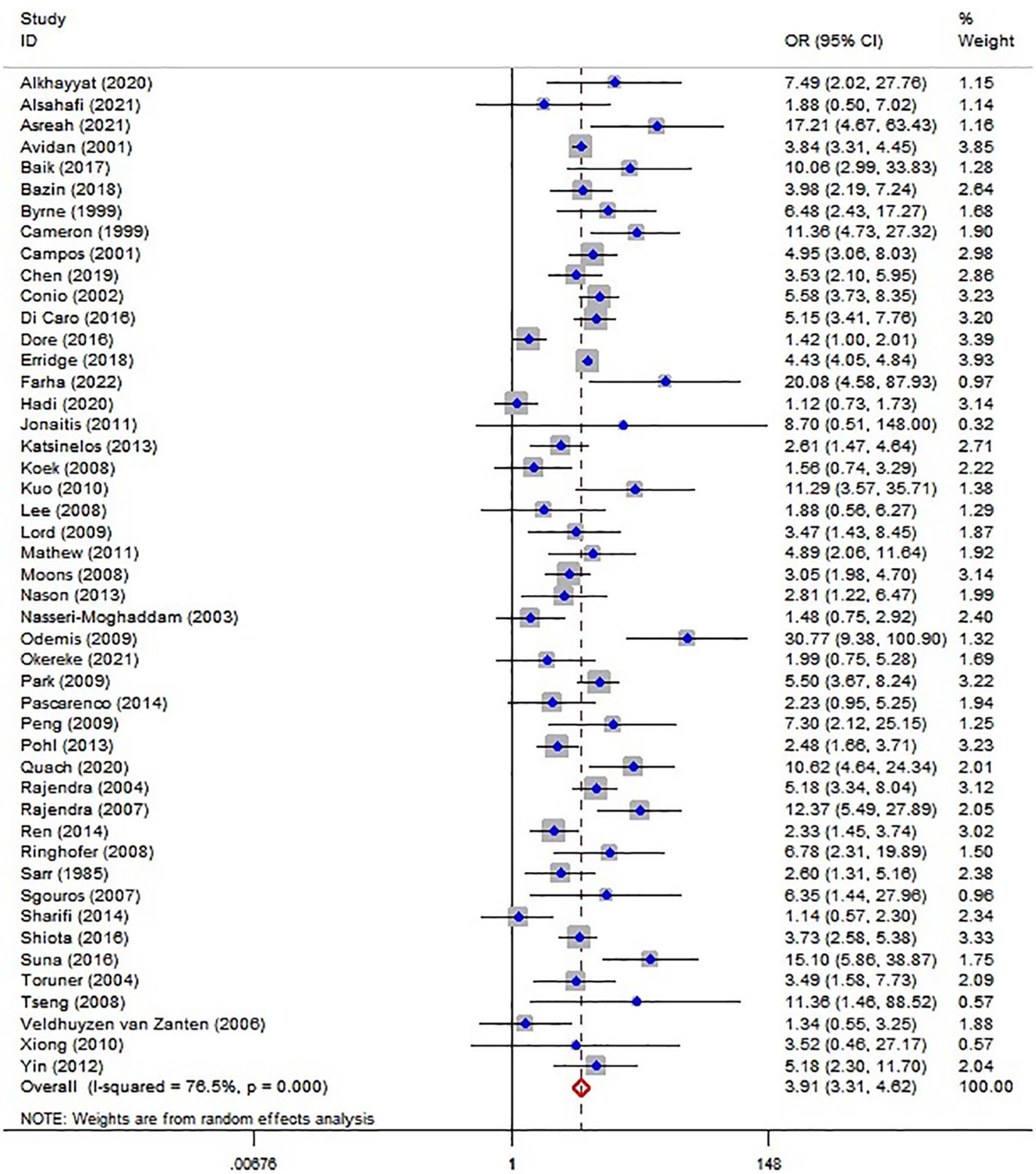

Figure 2. Forest plots showing the association of hiatal hernia with any length BE based on unadjusted data. BE, Barrett's esophagus.

studies (OR = 5.92, 95% CI = 0.58–60.36, $p = 0.13$), but remained in others. The interaction between subgroups was only significant in the subgroup analysis according to the definition of controls ($p = 0.005$), but not in others. A high level of heterogeneity was observed between studies in all subgroups. Meta-regression analyses indicated that the definition of controls ($p = 0.014$) might be a potential contributor to heterogeneity (Supplemental Table 4). Leave-one-out sensitivity analyses showed that no single study influenced the overall result (Supplemental Table 5). Egger test did not show any significant publication bias ($p = 0.984$).

Table 2. Results of subgroup analyses regarding the association of hiatal hernia with BE in studies unadjusted for confounders.

Groups	Any length BE				LSBE				SSBE			
	OR (95% CI)	Heterogeneity		$P_{interaction}$	OR (95% CI)	Heterogeneity		$P_{interaction}$	OR (95% CI)	Heterogeneity		$P_{interaction}$
		I^2 (%)	p Value			I^2 (%)	p Value			I^2 (%)	p Value	
Total	3.91 (3.31–4.62, $p<0.001$)	77	<0.001		10.01 (4.16–24.06, $p<0.001$)	78	<0.001		2.76 (2.05–3.71, $p<0.001$)	30	0.201	
Definition of controls				***0.005***				***<0.001***				***0.008***
Without BE on endoscopy	3.82 (2.71–5.37, $p<0.001$)	80	<0.001		9.90 (0.62–158.95, $p=0.11$)	48	0.170		2.47 (1.18–5.15, $p=0.02$)	0	0.410	
GERD	3.27 (2.59–4.11, $p<0.001$)	67	<0.001		9.23 (3.71–22.99, $p<0.001$)	55	0.080		1.84 (1.24–2.74, $p=0.003$)	0	0.590	
No-GERD	9.92 (5.53–17.79, $p<0.001$)	79	<0.001		74.05 (21.63–253.55.99, $p<0.001$)	0	0.460		8.16 (2.96–22.52, $p<0.001$)	0	0.350	
NEJ	9.08 (1.26–65.51, $p=0.03$)	84	0.010		4.73 (3.77–5.93, $p<0.001$)	–	–		3.43 (2.88–4.08, $p<0.001$)	–	–	
Study design				0.940				0.300				***0.040***
Case–control	3.93 (3.18–4.87, $p<0.001$)	78	<0.001		14.00 (4.75–41.27, $p<0.001$)	87	<0.001		3.33 (2.83–3.92, $p<0.001$)	0	0.480	
Cross-sectional	3.98 (2.97–5.33, $p<0.001$)	76	<0.001		4.39 (0.65–29.80, $p=0.13$)	49	0.140		1.88 (1.12–3.14, $p=0.02$)	0	0.420	
Cohort	5.92 (0.58–60.36, $p=0.13$)	86	0.009		–	–	–		–	–	–	
Publication year				0.360				0.340				0.420
After 2010	3.69 (2.85–4.78, $p<0.001$)	81	<0.001		2.63 (0.16–42.77, $p=0.50$)	–	–		1.84 (0.67–5.06, $p=0.24$)	–	–	
Before 2010	4.34 (3.42–5.53, $p<0.001$)	67	<0.001		11.10 (4.36–28.23, $p<0.001$)	81	<0.001		2.84 (2.08–3.89, $p<0.001$)	33	0.190	
Region				0.490				0.980				0.690
Asia	4.65 (3.17–6.83, $p<0.001$)	71	<0.001		7.62 (0.42–138.44, $p=0.17$)	89	0.002		2.32 (0.80–6.75, $p=0.12$)	64	0.090	

(Continued)

Table 2. (Continued)

Groups	Any length BE				LSBE				SSBE			
	OR (95% CI)	Heterogeneity		$P_{interaction}$	OR (95% CI)	Heterogeneity		$P_{interaction}$	OR (95% CI)	Heterogeneity		$P_{interaction}$
		I^2 (%)	*p* Value			I^2 (%)	*p* Value			I^2 (%)	*p* Value	
Europe	3.85 (2.89–5.15, $p<0.001$)	81	<0.001		9.90 (0.62–158.95, $p=0.11$)	48	0.170		2.47 (1.18–5.15, $p=0.02$)	0	0.410	
America	3.44 (2.49–4.75, $p<0.001$)	77	<0.001		10.56 (3.52–31.65, $p<0.001$)	83	0.003		3.21 (2.54–4.06, $p<0.001$)	11	0.320	
Oceania	6.78 (2.31–19.89, $p<0.001$)	–	–		–	–	–		–	–	–	
Sample size				0.740				0.050				***0.040***
>500	3.84 (3.08–4.79, $p<0.001$)	83	<0.001		4.73 (3.77–5.93, $p<0.001$)	–	–		3.43 (2.88–4.08, $p<0.001$)	–	–	
<500	4.08 (3.08–5.42, $p<0.001$)	65	<0.001		12.61 (4.90–32.48, $p<0.001$)	59	0.030		2.29 (1.62–3.23, $p<0.001$)	0	0.500	
Diagnostic criteria for BE				0.630				0.840				0.610
IM	4.00 (3.19–5.01, $p<0.001$)	77	<0.001		9.10 (3.41–24.34, $p<0.001$)	75	0.008		3.07 (2.38–3.96, $p<0.001$)	14	0.320	
CM	4.55 (2.82–7.35, $p<0.001$)	75	<0.001		11.58 (1.35–98.99, $p=0.03$)	79	0.008		2.52 (1.23–5.15, $p=0.01$)	43	0.170	
Diagnostic timing of BE				0.190				***0.005***				0.100
Newly diagnosed	4.12 (2.25–7.55, $p=0.002$)	86	<0.001		1.67 (0.34–8.22, $p=0.53$)	–	–		1.45 (0.71–2.97, $p=0.31$)	–	–	
Previously diagnosed	7.97 (3.66–17.35, $p<0.001$)	78	<0.001		32.22 (8.71–119.20, $p<0.001$)	0	0.890		3.53 (1.63–7.62, $p=0.001$)	0	0.940	

Note: Bold italic font indicates statistically significant.
BE, Barrett's esophagus; CI, confidence intervals; CM, columnar metaplasia; GERD, gastroesophageal reflux disease; IM, intestinal metaplasia; LSBE, long-segment BE; NEJ, normal esophagogastric junction; OR, odds ratio; SSBE, short-segment BE.

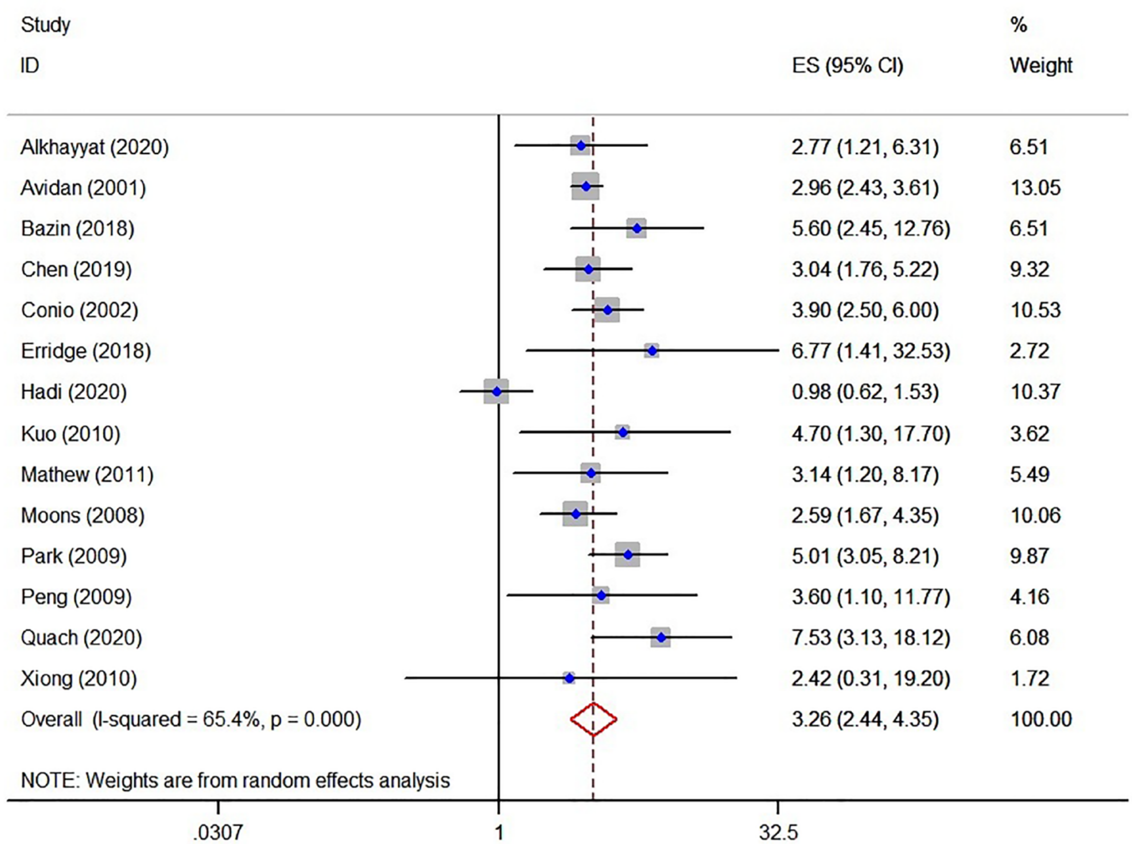

Figure 3. Forest plots showing the association of hiatal hernia with any length BE based on adjusted data.
BE, Barrett's esophagus.

Based on the adjusted data from six case–control and eight cross-sectional studies, the meta-analysis demonstrated a significantly higher prevalence of hiatal hernia in patients with BE than those without (aOR = 3.26, 95% CI = 2.44–4.35, $p < 0.001$). The heterogeneity was statistically significant ($I^2 = 65\%$; $p < 0.001$) (Figure 3). TSA could not be carried out owing to the inability to extract the prevalence rate in multivariate regression models. Results of subgroup analyses were shown in Table 3. Such a statistically significant association between them disappeared in the subgroup analyses of studies performed in America (OR = 1.98, 95% CI = 0.90–4.39, $p = 0.09$), but remained in others. The interaction between all subgroups was not significant. A high level of heterogeneity was observed between studies in all subgroups. Meta-regression analyses did not identify any source of heterogeneity (Supplemental Table 6). The heterogeneity significantly decreased after omitting the study by Hadi *et al.*[54] ($I^2 = 0\%$; $p = 0.44$), indicating that this study might be a potential contributor to heterogeneity (Supplemental Table 7). Egger test did not show any significant publication bias ($p = 0.416$).

Hiatal hernia and long-segment BE (LSBE)

Seven studies explored *the association between* hiatal hernia and LSBE. There was a significantly higher prevalence of hiatal hernia in patients with LSBE than those without BE (OR = 10.01, 95% CI = 4.16–24.06, $p < 0.001$). The heterogeneity was statistically significant ($I^2 = 78\%$; $p < 0.001$) (Figure 4). According to TSA, the cumulative *Z*-curves crossed the conventional test boundary and TSA boundary, and the total sample size surpassed the RIS ($n = 722$) as well, indicating that there was enough evidence to conclude a significant association of hiatal hernia with an increased risk of LSBE (Supplemental Figure 2). Such a statistically significant association between them disappeared in the subgroup

Table 3. Results of subgroup analyses regarding the association of hiatal hernia with BE in studies adjusted for confounders.

Groups	Any length BE			
	aOR (95% CI)	Heterogeneity		$P_{interaction}$
		I^2 (%)	*p* Value	
Total	3.26 (2.44–4.35, $p < 0.001$)	65	<0.001	
Definition of controls				0.720
Without BE on endoscopy	3.06 (1.64–5.71, $p < 0.001$)	80	<0.001	
GERD	3.29 (2.34–4.61, $p < 0.001$)	0	0.430	
No-GERD	3.90 (2.50–6.08, $p < 0.001$)	–	–	
NEJ	2.96 (2.43–3.61, $p < 0.001$)	–	–	
Study design				0.210
Case–control	2.82 (1.80–4.43, $p < 0.001$)	81	<0.001	
Cross-sectional	3.97 (3.00–5.25, $p < 0.001$)	0	0.650	
Publication year				0.990
After 2010	3.32 (1.91–5.77, $p < 0.001$)	72	<0.001	
Before 2010	3.30 (2.66–4.10, $p < 0.001$)	26	0.250	
Region				0.230
Asia	4.16 (3.09–5.59, $p < 0.001$)	0	0.640	
Europe	3.60 (2.52–5.15, $p < 0.001$)	24	0.270	
America	1.98 (0.90–4.39, $p = 0.09$)	89	<0.001	
Sample size				0.270
>500	3.09 (2.24–4.26, $p < 0.001$)	71	<0.001	
<500	4.44 (2.53–7.80, $p < 0.001$)	0	0.670	
Diagnostic criteria for BE				0.280
IM	3.00 (2.22–4.07, $p < 0.001$)	68	<0.001	
CM	4.98 (2.11–11.71, $p < 0.001$)	42	0.190	
Confounders adjusted				0.750
Full adjusted[a]	3.64 (1.58–8.42, $p = 0.002$)	82	<0.001	
Not full adjusted	3.17 (2.73–3.67, $p < 0.001$)	0	0.600	

[a]Full adjusted: at least age, gender, reflux symptoms, smoking, BMI, and/or waist circumference were adjusted.
aOR, adjusted odds ratio; BE, Barrett's esophagus; CI, confidence intervals; CM, columnar metaplasia; GERD, gastroesophageal reflux disease; IM, intestinal metaplasia; NEJ, normal esophagogastric junction.

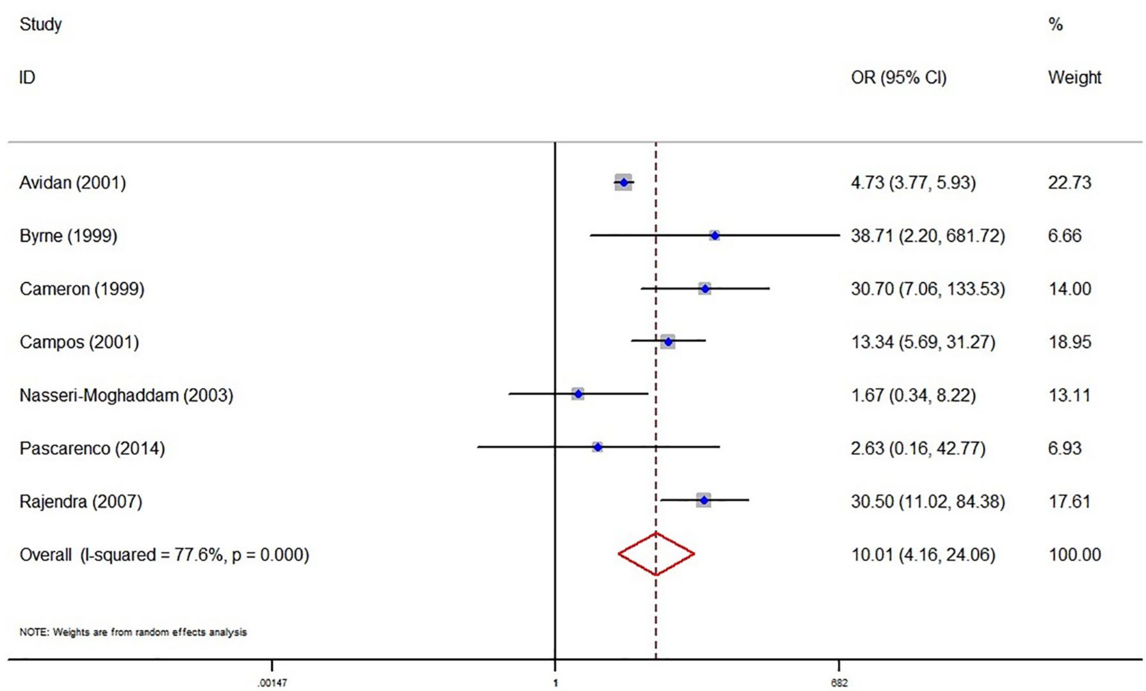

Figure 4. Forest plots showing the association of hiatal hernia with LSBE.
LSBE, long-segment Barrett's esophagus.

analyses of cross-sectional studies (OR = 4.39, 95% CI = 0.65–29.80, $p = 0.13$), those regarding patients without BE on endoscopy as the control group (OR = 9.90, 95% CI = 0.62–158.95, $p = 0.11$), those published after 2010 (OR = 2.63, 95% CI = 0.16–42.77, $p = 0.50$), those performed in Europe (OR = 9.90, 95% CI = 0.62–158.95, $p = 0.11$), and those which included newly diagnosed BE (OR = 1.67, 95% CI = 0.34–8.22, $p = 0.53$), but remained in others. The interaction between subgroups was statistically significant in the subgroup analyses according to the definition of controls ($p < 0.001$) and diagnostic timing of BE ($p = 0.005$), but not in others. Among the subgroup analyses, the heterogeneity remains substantial (Table 2). Meta-regression analyses did not find any source of heterogeneity (Supplemental Table 4). Leave-one-out sensitivity analyses showed that no single study influenced the overall result (Supplemental Table 8). Egger test did not show any significant publication bias ($p = 0.210$).

Hiatal hernia and short-segment BE (SSBE)

Seven studies explored the association between hiatal hernia and SSBE. There was a significantly higher prevalence of hiatal hernia in patients with SSBE than those without BE (OR = 2.76, 95% CI = 2.05–3.71, $p < 0.001$). The heterogeneity was not significant ($I^2 = 30\%$; $p = 0.201$) (Figure 5). According to TSA, the cumulative Z-curves crossed the conventional test boundary and TSA boundary, and the total sample size surpassed the RIS ($n = 583$) as well, indicating that there was enough evidence to conclude a significant association of hiatal hernia with an increased risk of SSBE (Supplemental Figure 3). Such a statistically significant association between them disappeared in the subgroup analyses of studies published after 2010 (OR = 1.84, 95% CI = 0.67–5.06, $p = 0.24$), those performed in Asia (OR = 2.32, 95% CI = 0.80–6.75, $p = 0.12$), and those which included newly diagnosed BE (OR = 1.45, 95% CI = 0.71–2.97, $p = 0.31$), but remained in others. The interaction between subgroups was statistically significant in the subgroup analyses according to the definition of controls ($p = 0.008$), study design ($p = 0.040$), and sample size ($p = 0.040$), but not in others (Table 2). Egger test did not show any significant publication bias ($p = 0.261$).

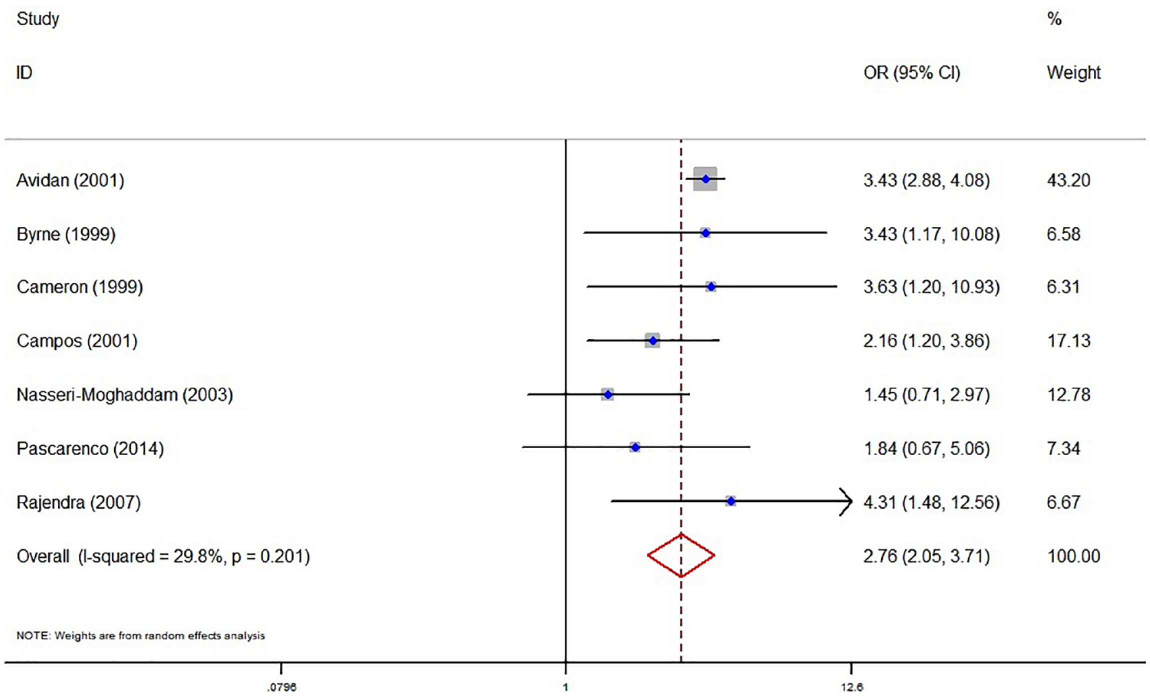

Figure 5. Forest plots showing the association of hiatal hernia with SSBE.
SSBE, short-segment Barrett's esophagus.

Discussion

The current practice guidelines do not consider the presence of hiatal hernia as a risk factor for BE1, 5–8. Our meta-analysis comprehensively searched relevant studies to explore the association of hiatal hernia with BE. We found that the presence of hiatal hernia was associated with a 3.91-fold increased risk for any length BE, a 10.01-fold increased risk for LSBE, and a 2.76-fold increased risk for SSBE. This association between hiatal hernia and BE remained significant even after adjustment for potential confounders, suggesting that hiatal hernia should be a significant risk factor for BE.

Currently, only one previous meta-analysis regarding the association between hiatal hernia and BE was published.[11] By comparison, our current meta-analysis had some advantages. First, the final search date was updated to retrieve a more comprehensive collection of eligible studies. Second, TSA was performed by minimizing random errors to evaluate the reliability and conclusiveness of conventional meta-analyses, which has not been conducted in the previous meta-analysis yet. Third, more subgroup analyses were carried out to further explore the association between hiatal hernia and BE according to the seven pre-specified baseline subgroups, and tests of interaction were also performed to establish whether the subgroups differed significantly from one another, which has not been performed in the previous meta-analysis yet. Fourth, meta-regression analyses for variables between studies were used to explore the potential causes of heterogeneity in our meta-analysis, but have not been done in the previous meta-analysis yet. Fifth, it is commendable that the selection criteria in our meta-analysis were more rigorous and plausible. Specifically, the participants included in control groups should not have endoscopically suspected BE or an irregular *Z* line. This consideration was very essential to avert the influences of these potential confounding factors on the reliability of our findings. Such selection criteria have not been employed by the previous meta-analysis, resulting in the inclusion of five ineligible studies.[66–70]

The pathogenesis of BE is primarily attributed to the impairment of the anti-reflux barrier, which leads to the exposure of esophageal mucosa to gastric and bile acids, resulting in damage to esophageal mucosa.[71,72] The causal role of hiatal hernia in an increased risk of BE may be explained by increased acid reflux due to the incompetence of gastroesophageal junction (GEJ), delay of esophageal acid clearance, and increased frequency of transient lower esophageal sphincter relaxations (tLESRs).

The first mechanism should be impaired GEJ function, as follows: (1) Gastroesophageal flap valve (GEFV), an important part of anti-reflux barrier, is a 180° musculomucosal fold formed by the intraluminal extension of the angle of His, which functions as a one-way valve.[73] Loss of the angle of His caused by hiatal hernia can impair the function of GEFV, and then promote reflux.[74] (2) Hiatal hernia may displace the lower esophageal sphincter (LES) proximally, and resting LES pressure can decrease with increasing displacement, thereby promoting reflux.[75] (3) A large hiatal hernia may widen the diaphragmatic hiatus, which weakens the ability of the crural diaphragm to function as an external sphincter, leading to the occurrence of reflux.[76]

The second is delayed esophageal acid clearance, as follows: (1) Gastric and bile acids may be trapped in hiatal hernia sac that acts as a reservoir, and then reflux proximally into the esophagus during a swallow-induced LES relaxation.[77,78] This sequence can be repeated, resulting in significantly delayed esophageal acid clearance.[76] (2) A large hiatal hernia may decrease the peristaltic wave amplitude and frequency in distal esophagus which is associated with delayed esophageal acid clearance.[79,80]

The third is tLESRs, a physiological phenomenon during digestion mediated *via* vagal pathways.[81] The presence of hiatal hernia is associated with a reduced threshold for eliciting tLESRs, increasing the frequency of tLESRs, which finally results in prolongation of esophageal acid exposure.[82]

In addition, esophageal injury caused by BE may lead to esophageal shortening and fibrosis, which may increase the size of hiatal hernia and worsen existing anti-reflux dysfunction,[83,84] and then further aggravates reflux.

We also found a more significant association of hiatal hernia with LSBE compared with SSBE. It seems obvious that LSBE has a greater esophageal acid exposure than SSBE.[85,86] This phenomenon may be attributed to the difference in their pathogenesis where LSBE may have a significantly lower LES pressure and a worse function of esophageal peristalsis primarily caused by hiatal hernia than SSBE.[87–89] Hence, LSBE may be more affected by acid reflux attributed to hiatal hernia and demonstrate a stronger association with hiatal hernia.

Our meta-analysis had several limitations. First, a majority of the included studies were retrospective, which inevitably leads to selection bias and recall bias, and a cause–effect relationship between hiatal hernia and BE could not be established due to the inherent weakness of retrospective study design. Second, the heterogeneity among studies regarding the association of hiatal hernia with LSBE was significant, in spite of leave-one-out sensitivity analyses and meta-regression analyses. Third, only some of included studies adjusted the confounders in multivariate regression analyses, and the confounders adjusted were inconsistent among them. Fourth, the association of hiatal hernia with BE was not the primary objective in most of the included studies. The diagnosis of hiatal hernia was based on endoscopy only, which may result in missed diagnoses of some small hiatal hernia or misdiagnosis of hiatal hernia caused by episodes of retching during endoscopy,[10] thereby underestimating or overestimating the effect of hiatal hernia on BE, respectively. Fifth, the information regarding the size of hiatal hernia was limited. In detail, only two studies reported the length of hiatal hernia,[58,62] and only three studies reported the number of different sized hiatal hernia grouped by different classification criteria in patients with and without BE.[51,55,56] Therefore, the effect of the size of hiatal hernia on BE could not be explored by subgroup analyses. Sixth, the absence of detailed information on the type of hiatal hernia prevented from further analysis regarding the association between subtypes of hiatal hernia and BE. Seventh, our meta-regression analyses indicated that the definition of control group might be a potential contributor to heterogeneity. Specifically, as shown in Table 2, our subgroup analyses demonstrated that the association of hiatal hernia with BE was weaker in the control group of GERD than the control group of non-GERD. These findings suggested that the association of hiatal hernia with BE might be dependent upon the presence of GERD. Indeed, a recent meta-analysis by Eusebi *et al*.[90] also indicated that hiatal hernia should be the strongest risk factor for the presence of BE in patients with GERD. Therefore, it is unclear about whether hiatal hernia is indirectly associated with BE by increasing the risk of GERD or directly involved in the development of BE in GERD patients.

Conclusion

The current evidence supports a close relationship between hiatal hernia and an increased risk of BE, which remains after adjusting for confounders. Additionally, hiatal hernia seems to correlate more strongly with LSBE compared with SSBE. More large-scale prospective cohort studies are required to confirm our findings in future.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have made an intellectual contribution to the manuscript and approved the submission.

Author contributions

Shaoze Ma: Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Zhenhua Tong: Formal analysis; Methodology; Writing – review & editing.

Yong He: Data curation; Formal analysis; Methodology; Writing – review & editing.

Yiyan Zhang: Data curation; Formal analysis; Methodology; Writing – review & editing.

Xiaozhong Guo: Formal analysis; Methodology; Supervision; Writing – review & editing.

Xingshun Qi: Conceptualization; Formal analysis; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data sharing is not applicable to this article as no new data were created in this study.

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Supplemental material

Supplemental material for this article is available online.

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